(b) cleaving the expressed fusion protein resulting from step (a) with cyanogen bromide, thereby producing mini-proinsulin; and

(c) incubating the mini-proinsulin of step (b) with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present.--

REMARKS

I. Obviousness-type Double Patenting Rejection

The Examiner has rejected claim 6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 17 of U.S. Patent No. 5,227,293 ("the '293 patent"). Specifically, the Examiner has alleged that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because claim 6 of the instant application is drawn to production of any fusion protein of mini-proinsulin followed by cleavage." Office Action at page 2, lines 26-30. According to the Examiner, claim 17 is drawn to a method of producing a specific fusion protein of mini-proinsulin with a cleavable site. Office Action at page 2, lines 30-31. Applicants respectfully traverse this rejection.

It has been established that "[i]t is the claims, not the specification, that define the invention ... [a]nd it is the claims that are compared when assessing double patenting." Ortho Pharmaceutical Corp. v. Smith, 959 F.2d 936 (Fed. Cir. 1992). Claim 17 of the '293 patent, which depends from claim 16 and ultimately from claim 1, recites a distinct process for the preparation of a fusion protein which contains a desired protein

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(i.e., a proinsulin in which the C chain consists of arginine) and a ballast constituent. The process of claim 17 comprises constructing a mixed oligonucleotide which codes for the ballast constituent wherein the oligonucleotide contains the DNA sequence, $(DCD)_x$, and the gene for the C chain, consisting of arginine, is designed so that it can be split off together with the ballast constituent. See claim 16 on which claim 17 depends.

Applicants have cancelled claim 6 of the instant application. New claim 2, which incorporates the subject matter of cancelled claim 6, does not claim a process which utilizes the DNA sequence, $(DCD)_x$. Moreover, claim 2 recites a distinctly different process in which the C chain, in the form of Arg, remains as part of formula I, i.e., it is not split off together with the ballast constituent.

Claim 17 of the '293 patent does not teach or suggest the distinct process of claim 2 for the preparation of a compound of the formula I in which if the gene structure also encodes a fusion protein, the compound of formula I, including the C chain, is liberated from the fusion protein. Therefore, as the processes of new claim 2 and claim 17 are patentably distinct, this rejection is in error and should be withdrawn.

II. Rejections Under 35 U.S.C § 103

The Examiner has rejected claims 1 and 6-9 under 35 U.S.C. § 103 as being unpatentable over either Markussen et al., U.S. Patent No. 4,916,212 ("the '212 patent), or Markussen et al.,

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EPO 163,529 ("the '529 patent). Applicants respectfully traverse this rejection.

Specifically, at page 3, lines 7-20, the Examiner has stated that:

> Markussen et al. ('212) discloses and claims insulin precursors of the form B(1-29)-X_n-Y-A(1-21). "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and "Y" is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. A preferred embodiment is B(1-29)-Ser-Lys-A(1-21). This precursor protein is a single peptide chain. This precursor is converted to human insulin by derivatization and treatment with trypsin ... Fusion proteins and their cleavage from the precursor are disclosed ... DNA sequences encoding the insulin precursor, expression vectors, transformed yeast cells, and recombinant methods of production in yeast are also disclosed and claimed.

The Examiner concludes that:

> Markussen et al. suggests the claimed mini-proinsulin precursor, DNA sequences encoding it, vectors, host cells and process for preparation where "X" is Thr, "n" is 1, and "Y" is Arg ... The claimed generic formula of the prior art encompasses applicant's claimed composition.

Office Action at page 4, lines 4-9. Applicants respectfully disagree.

In order to set forth a legally sufficient prima facie case of obviousness, the Examiner must show that the references teach or suggest the claimed invention with a reasonable expectation of success. In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988). This the Examiner has failed to do.

Applicants have cancelled claims 1 and 6-9 and incorporated the subject matter of those claims into new claims 1-5. With respect to the '212 patent, Applicants maintain, while

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incorporating herein the arguments made at pages 6-9 of the Response dated May 24, 1993, that despite the '212 patent's disclosure of the formula $B(1-29)-(X_n-Y)_m-A(1-21)$, the Examiner has still not shown that the '212 patent teaches Applicants' claimed formula I with a reasonable expectation of success.[1/] As the Examiner has noted, the '212 patent teaches that certain amino acids and integers can be substituted for X, n, Y, and m in the above formula. However, even if, arguendo, these teachings taught or suggested Applicants' claimed invention, Applicants maintain that there is an extremely low probability that one skilled in the art, relying on these teachings, would pick and choose from all of the possibilities presented that combination necessary to arrive at Applicants' claimed formula I.

First, in order to obtain Applicants' claimed invention, X must be Thr. As the '212 patent teaches that X may preferably be selected from the group consisting of Ala, Ser, and Thr (i.e., X could be chosen from other amino acids), there is at most a 1 in 3 (1/3) chance that one skilled in the art would substitute Thr for X. Also, as n is an integer from 1-33, there is only a 1 out of 33 (1/33) chance that one skilled in the art would substitute 1 for n in order to obtain Applicants' claimed invention.

[1/] The Examiner has stated at page 3, lines 21-23, of the Office Action that Markussen et al. (the '529 patent) teaches essentially the same invention as the '212 patent. Therefore, in addressing the Examiner's rejection of claims 1 and 6-9 (now claims 1-5), Applicants' arguments will apply equally to the '212 patent and the '529 patent.

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Finally, with respect to Y and m, there is a 50% chance for both (i.e., 1/2) that one skilled in the art would substitute Arg for Y and 1 for m. Therefore, in total, there would only be roughly a 1 out of 400 (1/400) chance that one skilled in the art would pick and choose that combination necessary to arrive at Applicants' claimed invention from all of the possibilities presented. Applicants maintain that a 1/400 chance does not amount to a reasonable expectation of success as required by Dow Chemical.

In addition to the requirement that a reference teach a reasonable expectation of success, the prior art must provide motivation to make the proposed modifications needed to arrive at the claimed invention. In re Lalu, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). In this case, however, the '212 patent would not provide such motivation. The '212 patent teaches that the preferred insulin precursors of the formula are B(1-29)-A(1-21), B(1-29)-Ser-Lys-A(1-21), and B(1-29)-Ala-Ala-Lys-A(1-29) (i.e., it teaches preferred insulin precursors in which the C chain does not consist of a single amino acid, Arg). See column 3, lines 8-9 and 16-17. In light of these preferred compounds, and in light of the fact that the '212 patent does not teach or suggest that Applicants' Thr-Arg compounds result in advantageous processing to mono-Arg insulin, there would be no motivation for one skilled in the art to pursue, out of all the other choices, Applicants' claimed Thr-Arg compound.[2/]

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2/ As the '212 patent does not teach or suggest Applicants' claimed formula I with a reasonable expectation of success, it cannot teach or suggest the DNA, gene structure or plasmid, or

(footnote continued)

Recently, the Federal Circuit issued a decision in In re Baird, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994), which clearly invalidates the position taken by the Examiner with respect to the alleged obviousness of Applicants' formula I in light of the '212 patent. In Baird, the Examiner rejected the applicant's claim 1 which recited bisphenol A polyester on the grounds that it was obvious in light of Knapp et al. Knapp et al., which recited a generic formula with a broad range of variables, encompassed a large number of different diphenols, one of which was bisphenol A.

The Federal Circuit, in reversing the rejection of the applicant's claim, stated that the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. Baird, 29 U.S.P.Q.2d at 1552. Further, according to the Court:

> [w]hile the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables. Indeed, Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols.

Id.

According to the Court, "[a] reference must be considered not only for what it expressly teaches, but also for what it fairly suggests." Id. Thus, the Court concluded that:

> given the vast number of diphenols encompassed by the generic diphenol formula in Knapp, and the fact that the diphenols that Knapp specifically discloses to be

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(cont'd)
bacterium of dependant claims 7-9 (now claims 3-5) with a reasonable expectation of success.

> 'typical,''preferred,' and 'optimum' are different from and more complex than bisphenol A, we conclude that Knapp does not teach or fairly suggest the selection of bisphenol A. Baird at 1552 (emphasis added).

Given the vast number of insulin precursors encompassed by the generic formula recited in the '212 patent, and given the fact that the preferred insulin precursors specifically disclosed by the '212 patent differ markedly from Applicants' claimed compound of formula I at the C chain (see Applicants' argument above at pages 11-12), the '212 patent, under Baird, neither teaches nor fairly suggests the selection of Applicants' claimed formula I.

In addition to not teaching or suggesting Applicants' formula I with a reasonable expectation of success, the '212 patent also does not teach or suggest either the fusion protein or the bacterium recited in claim 6 (now claim 2). Applicants maintain that the additional amino acid sequence adjacent to the N-terminal of the B(1-29) chain referred to at column 5, lines 11-20, of the '212 patent is a leader sequence that is required for the secretion of the expressed protein product from the yeast cells disclosed in the '212 patent.

The instant invention, which claims the use of bacterium as opposed to yeast cells, does not require the use of a leader sequence for the secretion of protein. In the claimed invention, the ballast component causes the fusion proteins to precipitate as inclusion bodies in E. coli. Therefore, as this teaching of a leader sequence in the '212 patent is not tantamount to a teaching or suggestion of the fusion protein recited in claim 6 (new claim 2), the Examiner has failed to

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show that either the '212 patent or the '529 patent teaches or suggests Applicants' claimed invention with a reasonable expectation of success. Thus, the Examiner's rejection of claims 1 and 6-9 (now claims 1-5) is in error and should be withdrawn.

The Examiner has rejected claim 6 under 35 U.S.C. § 103 as being unpatentable over Markussen et al., EPO 163,529 ("the '529 patent) or Markussen et al., U.S. Patent No. 4,946,828 ("the '828 patent") either in view of Goeddel et al., EPO 055,945 ("Goeddel"). Office Action at page 4, lines 13-16. Applicants respectfully traverse this rejection.

The Examiner has stated that he has applied both Markussen et al. references as above. However, Applicants note that this is the first time in the Office Action that the Examiner has cited the '828 patent and, thus, he has not characterized or applied the reference in support of this rejection. Therefore, the undersigned cannot respond to this rejection or those that follow over the '828 patent.

With respect to Goeddel, the Examiner states that Goeddel teaches producing recombinant fusion proteins of insulin precursors fused to another protein and cleaving them. Office Action at page 4, lines 18-19. Thus, according to the Examiner, "[i]t would have been obvious to make fusion proteins as taught by Goeddel et al. using the insulin precursor, DNA sequences, and vectors taught by either Markussen et al. reference." Office Action at the bottom of page 4 and the top of page 5. Applicants respectfully disagree.

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"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." In re Geiger, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987). The Examiner has not shown or alleged any teaching or suggestion from any one or more of the cited references from which one skilled in the art would have been motivated to combine either Markussen reference with Goeddel in order to obtain Applicants' claimed invention.

First, with respect to the '529 patent in view of Goeddel, the '529 patent teaches essentially the same invention as the '212 patent. Like the '212 patent, the '529 patent fails to teach or suggest Applicants' claimed formula I with a reasonable expectation of success. Further, it does not teach or suggest fusion proteins or the use of bacterium as recited in Applicants' claim 6 (now claim 2).

Goeddel teaches away from the instant invention by disclosing a process for producing a chimeric polypeptide comprising the polypeptide sequence of a proinsulin comprising the A and B chains of human insulin connected by a bridging chain of at least 2 amino acids units and an additional protein or protein fragment. Goeddel does not teach or suggest the use of its process for producing a chimeric polypeptide with insulin precursors of the formula I disclosed by the '529 patent.

In attempting to supply the necessary motivation to combine, the Examiner has argued that "[o]ne would have been motivated by the known benefits of producing small peptides as fusion

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proteins in bacterial and yeast hosts and the success with another insulin variant in which the C chain is shortened. Office Action at page 5, lines 3-6. However, Applicants note that even Markussen et al., who knew of Goeddel (see the '529 patent at page 3, lines 22-24), apparently were not motivated to combine the various teachings in order to obtain Applicants' claimed invention. In fact, a stated object of the '529 patent is the circumvention of the disadvantages of Goeddel and other earlier endeavors to provide biosynthetic insulins. See the '529 patent at page 4, lines 14-19.

Given Goeddel's teaching of a bridging chain of at least 2 amino acids and the '529 patent's teaching that preferably the bridging chain in formula I contains from 2 to 8 amino acid residues, see the abstract of the '529 patent, the Examiner has not shown why one skilled in the art would have been motivated to combine the teachings of Goeddel and the '529 patent to arrive at Applicants' claimed process for the preparation of a compound in which the bridging chain between the unshortened A and B chains is only one arginine residue.

Even if, arguendo, the references were properly combined, the combination would not have taught or suggested Applicants' claimed invention with a reasonable expectation of success. As already established, the '529 patent is equally as deficient as the '212 patent with respect to the teaching of the instant invention. Further, Goeddel, which does not teach or suggest any formula at all for an insulin precursor, cannot overcome the deficiencies of the '529 patent.

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The Examiner has rejected claim 10 under 35 U.S.C. § 103 as being unpatentable over the '529 patent or the '828 patent, either in view of Goeddel and Mai et al., U.S. Patent No. 5,087,564 ("Mai"). Office Action at page 5, lines 10-13. Applicants respectfully traverse this rejection.

The Markussen et al. '529 reference[3/] and Goeddel are applied as above. With respect to Mai, the Examiner states that Mai teaches that it would have been well known in the art to use common cleavage sites in fusion proteins. Thus, the Examiner concludes that:

> [i]t would have been obvious to make the miniproinsulin of Markussen et al. as a fusion protein using the cleavable sequence Met-Ile-Glu-Gly-Arg. Markussen et al. suggests making fusion proteins that can be cleaved as does Goeddel et al. The recited sequence includes cleavage sites for cyanogen bromide and factor Xa that would have been commonly used in fusion proteins.

Office Action at the bottom of page 5 and the top of page 6. Applicants respectfully disagree.

Applicants incorporate herein all of the arguments made previously with respect to the '529 patent and Goeddel. With respect to Mai, Applicants maintain that Mai also fails to provide the necessary motivation to combine.

Mai teaches a method for obtaining heterologous peptides from fusion proteins by site-specific cleavage with an endopeptidase wherein heterologous peptides include eucaryotic hormones such as atrial peptides. Applicants acknowledge the

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3/ For the reasons given above, the undersigned does not have enough information regarding the application of the '828 patent to the claimed invention to respond to the Examiner's rejection.

Examiner's statement at page 5, lines 17-20, of the Office Action regarding cyanogen bromide and factor Xa cleavage. However, Mai never teaches or suggests the use of the disclosed cleavage sites in fusion proteins which contain peptide chains with the formula $B(1-29)-(X_n-Y)_m-A(1-21)$ such as is disclosed in the '529 patent.

Therefore, there would be no motivation for one skilled in the art to combine the teachings of the cited references in order to arrive at Applicants' claimed invention. At most, it might be "obvious to try" combining the various teachings. However, "obvious to try" is not the proper standard under § 103. In re Fine, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988).

Even if, arguendo, Mai provided the necessary motivation to combine, the combination would not have taught or suggested Applicants' claimed invention. Applicants have cancelled claim 10 and incorporated the subject matter into new claim 9. Claim 9 recites a fusion protein which comprises the compound of the formula I bonded via a bridging member, Met - Ile - Glu - Gly - Arg, to a peptide which stabilizes the fusion protein. Mai does not teach or suggest a compound of the formula I, nor does it teach or suggest the use of Applicants' claimed bridging member made up of a methionine residue linked to the sequence, Ile-Glu-Gly-Arg. Thus, as Mai cannot overcome the deficiencies of the other references, the Examiner's rejection of claim 10 (now claim 9) is in error and should be withdrawn.[4/]

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[4/] Applicants disagree with the Examiner's statement at the bottom of page 5 and the top of page 6 that "Markussen et al. suggests making fusion proteins that can be cleaved as does

(footnote continued)

The Examiner has rejected claims 12-13 and 15 under 35 U.S.C. § 103 as being unpatentable over the '529 patent or the '828 patent, either in view of Grau, U.S. Patent No. 4,801,684 ("the '684 patent") and Grau, U.S. Patent No. 4,639,332 ("the '332 patent"). Office Action at page 6, lines 7-11. Applicants respectfully traverse this rejection.

Specifically, the Examiner has argued that:

> [w]ith respect to claims 12 and 13, it would have been obvious to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. first to Mono-Arg insulin and then to insulin. Grau ('332) teaches that Mono-Arg insulin can be formed by trypsin cleavage ... and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin.

Office Action at the bottom of page 6 and the top of page 7.

With respect to claim 15, the Examiner has stated that:

> [i]t would have been obvious to prepare Mono-Arg insulin by expressing a DNA molecule encoding miniproinsulin in yeast as taught by Markussen et al. and cleaving this compound with trypsin as taught by Grau ('332 and '684) to produce Mono-Arg insulin.

Office Action at page 7, lines 11-15. Applicants respectfully disagree.

Applicants incorporate herein all of the arguments made previously with respect to the '529 patent.[5/] With respect to the '332 and '684 patents, Applicants maintain that both Grau

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Goeddel et al." None of these references refer to the fusion protein of the instant invention.

5/ See footnote 3 regarding the '828 patent.

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references fail to provide the necessary motivation to combine the references in the manner asserted by the Examiner.

The '332 patent teaches a process for the preparation of an insulin derivative of the formula I by splitting of proinsulin intermediates, proinsulin, preproinsulin, or analogs thereof, in the presence of at least one phenol (see claim 1 of the '332 patent). The '332 patent does not teach or suggest a process for the preparation of insulin precursors of the formula (I) claimed in the '684 patent (Grau) or of the formula I claimed in the '529 patent (Markussen). Moreover, the '332 does not teach or suggest a process for the preparation of any insulin precursor in the absence of a phenol or similar aromatic hydroxy compounds as does the instantly claimed invention.

The '684 patent teaches a process for the preparation of correctly-recombined insulin precursors of the formula (I) from reaction mixtures which result from folding of insulin precursors from S-sulfonates of the formula (II). The '684 patent does not teach or suggest a process for the preparation of the insulin derivatives of the formula I claimed in the '332 patent (Grau) or the insulin precursor of the formula I claimed in the '529 patent (Markussen).

Therefore, the Examiner has not shown why one skilled in the art would have been motivated to combine the teachings of the cited references in order to arrive at Applicants' claimed invention. The Examiner is merely picking select teachings from the cited references regarding trypsin and carboxypeptidase B to supply the necessary motivation to combine. However, Applicants

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maintain that these teachings, without more, do not provide the necessary motivation to combine.

Even if, arguendo, the '332 and the '684 patents provided the necessary motivation to combine with Markussen '529, the combination would not have taught or suggested Applicants' claimed invention. Without acquiescing in the propriety of the rejection, and solely to expedite prosecution, Applicants have cancelled claims 12-13 and incorporated the subject matter of these claims into new claims 7-8. Claim 7 recites a method for the preparation of insulin using the compound of the formula I which comprises: (a) expressing a DNA molecule encoding the compound of the formula I in a bacterium; (b) incubating the expressed compound of the formula I resulting from step (a) with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present; and (c) cleaving the resulting compound of the formula II with carboxypeptidase B.[6/]

Neither the '332 patent nor the '684 patent teaches or suggests a method in which a compound of formula I is incubated with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present. On the contrary, in the process of claim 1 of the '332 patent, the presence of at least one phenol is expressly required.

Moreover, without acquiescing in the propriety of the rejection, and solely to expedite prosecution, Applicants have

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6/ Support for this claim, as well as for new claim 8 and new claim 6, which will be discussed, infra, is found at page 15, lines 24-26, of the specification.

cancelled claim 15 and incorporated the subject matter of this claim into new claim 6. Claim 6 recites a method for the preparation of a compound of formula II ... using the compound of the formula I which comprises a) expressing a DNA molecule encoding the compound of the formula I in a bacterium; and b) incubating the expressed compound of the formula I resulting from step (a) with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present. Again, neither the '332 patent nor the '684 patent teaches or suggests a method in which a DNA molecule encoding the compound of formula I is expressed in a bacterium and in which the expressed compound of the formula I is incubated with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present.

Thus, as neither the '332 patent nor the '684 patent can overcome the deficiencies of either the '529 patent or the '828 patent, the Examiner's rejection of claim 12-13 and 15 (now claims 6-8) is in error and should be withdrawn.

The Examiner has rejected claim 14 under 35 U.S.C. § 103 as being unpatentable over Markussen et al., the '212 patent, or Markussen et al., the '529 patent, either in view of Goeddel et al., the '945 patent, Grau, the '684 patent, and Grau, the '332 patent. Office Action at page 7, lines 19-23. Applicants respectfully traverse this rejection.

First, Applicants maintain that for all of the reasons previously set forth in this Amendment, the Examiner has still not shown the necessary motivation to combine the references in the manner asserted. Moreover, even if, arguendo, the Examiner

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could establish the necessary motivation to combine, the combination would not have taught or suggested Applicants' claimed invention.

Without acquiescing in the propriety of the rejection, and solely to expedite prosecution, Applicants have cancelled claim 14 and incorporated the subject matter of this claim into claim 6. Claim 6 now recites in a step (b) incubating the expressed compound of the formula I resulting from step (a) with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present. As none of the cited references teaches or suggests a method in which the expressed compound of the formula I is incubated with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present, the cited references do not, and cannot, render claim 14 (now claim 6) obvious under 35 U.S.C. § 103. Therefore, this rejection is in error and should be withdrawn.

The Examiner has argued at page 9, lines 3-5, of the Office Action that a prima facie case of obviousness has been made for the compound of claim 1 over Markussen et al. However, for the reasons stated at pages 10-13 of this Amendment, Applicants respectfully disagree. The Examiner is reminded that under the patent laws it is not sufficient that Markussen et al. merely "contemplate" Applicants' compound of formula I. Instead, to render the claimed compound prima facie obviousness, Markussen et al. must teach or suggest the claimed compound with a reasonable expectation of success. This Markussen et al. fail to do. Therefore, as a prima facie case of obviousness has not

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been made out, Applicants maintain that they are not required to show unexpected results.

The Examiner has also argued at page 9, lines 14-18, of the Office Action that "[t]here is no evidence of record to show that the embodiments of Markussen et al. could not be used in the methods as claimed or that the miniproinsulin claimed is unexpectedly better in any way." First, Applicants respectfully note that the law does not place a burden on Applicants to show that the embodiments of Markussen et al. could not be used in Applicants' "one-pot reaction." Rather, Applicants need only show that Markussen et al. does not teach or suggest Applicants' advantageous one-pot reaction with a reasonable expectation of success.

Moreover, at pages 4-5 of the specification, Applicants have demonstrated that the claimed compound of formula I possesses an advantageous property not previously taught or suggested by the prior art in that the compound of formula I can be converted to insulin in a surprisingly simple "one-pot reaction."

The Examiner has stated that "[i]t is noted with respect to the stated advantages of the claimed miniproinsulin in a 'one-pot' reaction in the amendment after final rejection that the specification does not exemplify a method ... where [the] two steps are carried out in one vessel without having to isolate mono-Arg insulin." Office Action at the bottom of page 9 and the top of page 10.

As stated at page 15 of the May 24, 1993, Proposed Amendment After Final, the number and variety of examples are irrelevant if the disclosure is enabling and sets forth the best mode

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contemplated. In re Borkowski, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Therefore, Applicants do not need to provide even one example in which a "one-pot" reaction is performed.

Further, the Examiner has argued that "[w]hile the specification generally states that the trypsin and carboxypeptidase can be administered simultaneously, this has not been demonstrated nor shown to produce better results than a two-pot reaction or a one-pot reaction with the embodiments of Markussen et al." Office Action at page 10, lines 15-19. Applicants respectfully disagree.

Applicants have not alleged that the "one-pot reaction" necessarily produces "better results" than a two-pot reaction. Rather, it has been argued that the one-pot reaction utilizing the claimed compound of formula I is surprisingly more simple, and therefore economical, than a two-pot reaction.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 6-9 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite. Office Action at page 10, lines 21-24. Applicants respectfully traverse this rejection.

Specifically, the Examiner alleges that claim 7 and dependent claims 8-9 are confusing in reciting "compounds." Without acquiescing in the propriety of the rejection, and solely to expedite prosecution, Applicants have cancelled claim 7 and incorporated the subject matter of that claim into new claim 3. Claim 3 recites "compound." Therefore, the rejection

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of claims 7 and dependent claims 8-9 (now claims 3-5) has been overcome and should be withdrawn.

The Examiner has argued that claim 6 is confusing in reciting "if the gene structure encodes for a fusion protein." Office Action at page 11, lines 5-7. Applicants respectfully disagree.

Without acquiescing in the propriety of the rejection, and solely to expedite prosecution, Applicants have cancelled claim 6 and incorporated the subject matter of that claim into new claim 2. Claim 2 recites "and, if the gene structure also encodes a fusion protein..." (emphasis added). As claim 2 is not indefinite, this rejection has been overcome and should be withdrawn.

Finally, the Examiner has alleged that claim 14 is confusing in reciting "expressing a DNA molecule encoding the compound of formula I" and "when said compound of formula I is in the form of a fusion protein." Office Action at page 11, lines 10-12. Applicants respectfully disagree.

Without acquiescing in the propriety of the rejection, and solely to expedite prosecution, Applicants have cancelled claim 14 and incorporated the subject matter of that claim into new claim 6. As claim 6 does not refer to a fusion protein, claim 6 is not indefinite. Therefore, this rejection has been overcome and should be withdrawn.

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The Commissioner is hereby authorized to charge any additional fees (or credit any overpayment) associated with this communication to our Deposit Account No. 06-916. If a fee is required for an extension of time under 37 C.F.R. Section 1.136 not accounted for above, such extension is requested and should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

By: Carol P. Einaudi
Carol P. Einaudi
Reg. No. 32,220

Date: March 25, 1994

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